REMARKS

Claim 7 is currently pending in the present application.

REJECTIONS UNDER 35 U.S.C. §103(A)

Claim 7 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Condra *et al.* and Seki *et al.* and Bakhanashvili *et al.*

More specifically, the examiner holds the view (as he has throughout the prosecution of this matter) that Condra *et al.* addresses issues of resistance of HIV treatment to indinavir, an HIV protease inhibitor.

The examiner admits that Condra *et al.* do not teach or address resistance conferred by mutations in HIV reverse transcriptase as it addresses treatment with a protease inhibitor alone. However the examiner states that, as well accepted in the art, and as addressed in the Background section of the present application, the preferential HIV therapy includes combination of inhibitors of both PI and RT (reverse transcriptase); the latter can be also a combination of NNTRTI and NRTI. Therefore, it would be obvious to one skilled in the art at the time the invention was made to evaluate effectiveness of such combined anti-HIV therapy by determining presence of potential resistance to RT inhibitors.

The examiner holds the view that Seki *et al.* teach that resistance to NNRTIs is dependent on both the quality and the quantity of mutations within the HIV-1 RT gene, and, in particular point at mutation at 103 position to 103R which is related to development of the resistance (comparing this to claim 7, step (a)(2)). Further, the examiner states that Bakhanashvili *et al.* teach resistance to treatment by nucleoside analogs conferred by Met 184 to Leu mutation in RT, *i.e.*, another mutation addressed in the instant claim.

Therefore the examiner is of the opinion that one of skill in the art would be motivated to evaluate effectiveness of anti-HIV therapy by determining presence of potential resistances to both PI and RT inhibitors, *i.e.,* inhibitors used in combination as a part of routine HIV therapy. In the course of assessing potential mutations, an artisan would be motivated to determined to use the mutations described in Condra, Seki and Bakhanashvili as these mutations are some of the mutations conferring resistance to known HIV PI or RT inhibitors.

As is stated in M.P.E.P. §2143, three criteria must be met to establish *prima facie* obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention when there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one ordinary skill in the art. MPEP § 2143.01.

Here, a *prima facie* case of obviousness has not been established, at least because there is no suggestion or motivation to modify or to combine the references. Additionally, the references cited do not teach or suggest all the claim limitations. Indeed, it is only through impermissible hindsight that one could possibly derive the instant invention from the cited references.

The Condra reference is directed to a study of PI resistance. Table 1 of the reference provides a comprehensive summary of protease mutations found in viral isolates taken from 21 different patients. One patient, patient "O", displayed PI resistance when the combination of eight different mutations was present. The 88T mutation of the instant invention was one of the mutations present in this combination. This is the only place in the entire reference in which 88T appears. The examiner arrives at the conclusion that this table entry is enough to indicate that the presence of 88T in any combination of mutants as responsible for resistance. The examiner stated that "88T (i.e., the elected species) correlates with reduced effectiveness of antiviral therapy." No such correlation is shown in Condra nor has the examiner pointed to any "correlation".

On the contrary, Condra teaches something much different. Table 1 shows 29 different combinations of mutations in isolates that display PI resistance. Of these, 17

different combinations of mutations as found in isolates with an IDV CIC_{95} greater than or equal to 1500 nM. There are 12 different combinations of mutations found in isolates with an IDV CIC_{95} greater than or equal to 3,000 nM. There is only one isolate in which 88T appears and that occurs within a combination of eight different mutations. Assuming that one skilled in the art started with a list of the 12 different combinations of mutations correlating with the IDV CIC95 greater than or equal to 3,000 nM, the chances of selecting the 88T mutation as a marker whose presence correlates with PI resistance is statistically very large since one cannot be sure whether all mutations within a listed combination are necessary or sufficient to make such a correlation, whether only a subset if such mutations are necessary or sufficient, whether an individual mutation is necessary or sufficient (including whether 88T alone correlates with PI resistance), and which combination or which individual mutation from within the recited combination is necessary or sufficient to make such a correlation.

Even if one somehow concluded that they should consider a marker for PI resistance from the findings of patient O, the chance of identifying 88T as a marker of interest is very small since one must consider all combinations of the eight mutations as well as each one individually. Even Condra, in reviewing combinations more indicative of resistance than the one containing 88T, note "no invariant combination clearly coincided with the loss of inhibition susceptibility". Condra at col. 2, line 18, pp 8271. At best, Condra provides the basis for an obvious to try argument where there is far from anything like a reasonable likelihood of success. Of course, such an argument fails to provide the basis for an obviousness rejection. *In re O'Farrell*, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988).

Even given a reading most closely aligned with the examiner's position, Condra actually teaches away from the use of 88T as a PI resistance marker. In the Condra abstract, Condra states that

"No single substitution was present in all resistance isolates, indicating that resistance evolves through multiple genetic pathways. Despite this complexity, all of 29 resistant isolates tested exhibited alteration of residues M-46 (to I or L) and/or V-82 (to A, F, or T), suggesting that screening of these residues may be useful in predicting the emergence of resistance. We also extended our previous finding that IDV-resistant viral variants exhibit various patterns of cross-resistance to a divers panel of HIB-1 protease inhibitors. Finally, we noted an association between the number of protease amino acid substitutions and observed

level of IDV resistance." This shows the emphasis the investigators put on a discrete set of mutations that did not include 88T.

This emphasis is seen again in the second paragraph of column 2 of 8271, "An examination of the protease sequences in the viral isolates over time (Table 1) showed a high frequency of substitutions at several amino acid residues, especially...M-46(to I or L) ... V-82 (to A, F, or T)". Notably absent was any reference to 88T.

Therefore, the examiner's statement that, "[i]n the course of assessing potential mutations, an artisan would be motivated to determined (sic) to mutations described in Condra, Seki and Bakhanashvili as these mutations are some of the mutations conferring resistance to known HIV PI or RT inhibitors" is misplaced. Condra provides no motivation as described above.

It is clear that the motivation for the method of evaluating the effectiveness of an antiviral therapy of an HIV-infected patient of the present invention comes not from the cited references, *but from the application itself.* A proper *per se* obviousness rejection cannot rely on the application to find the motivation to modify the prior art, as this is a hallmark of impermissible hindsight reasoning. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). Moreover, the examiner must show reasons that the skilled artisan would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). The examiner made no such showing. As described above, Condra, in Table 1, shows 29 different combinations of mutations in isolates that display PI resistance. Of these, 17 different combinations of mutations as found in isolates with an IDV CIC_{95} greater than or equal to 1500 nM. There are 12 different combinations of mutations found in isolates with an IDV CIC_{95} greater than or equal to 3,000 nM. There is only one isolate in which 88T appears and that occurs within a combination of eight different mutations. The examiner has not enumerated the reasons a skilled artisan would select 88T from Table 1 in Condra. The chances of a skilled artisan selecting the 88T mutation as a marker whose presence correlates with PI resistance is statistically very large since one cannot be sure whether all mutations within a listed combination are necessary or sufficient to make such a correlation, whether only a subset if such mutations are necessary or sufficient, whether an individual mutation is necessary or sufficient (including whether 88T alone

correlates with PI resistance), and which combination or which individual mutation from within the recited combination is necessary or sufficient to make such a correlation

Thus, Applicants respectfully submit that a *prima facie* case of obviousness has not been set forth. In view of the foregoing, Applicants respectfully request that the rejection of the claim 7 under 35 U.S.C. § 103 be withdrawn.

35 U.S.C. § 112, FIRST PARAGRAPH/NEW MATTER OBJECTION

The amendment filed September 27, 2004, is objected to under 35 U.S.C. § 112, first paragraph, as lacking written description. More specifically, the examiner stated that he has not found "ipsis verbis" support for the limited subgenus in the specification and that Applicants have not indicated support in the specification for the subgenus as claimed. The examiner stated that "Applicant must cancel the new matter in response to the rejection."

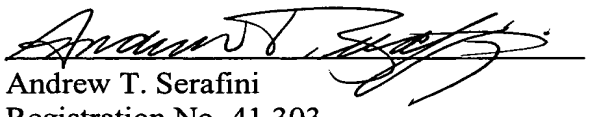
Applicants traverse the objection because a person skilled in the art would understand that the specification disclose this step. It is well-established that with respect to the specification, claim "terms need not be used in *haec verba*." *Koito Mfg. v. Turn-Key-Tech*, 381 F.3d 1142, 1154 (Fed. Cir. 2004). In determining whether a patentee has adequately described a claimed invention, the specification need only "allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described.'" *Koito Mfg.*, 381 F.3d at 1154 (citing *Biochem, Inc.*, 323 F.3d at 968) (quoting *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1573 (Fed. Cir. 1997); *see also Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003)). Indeed, claim limitations may be supported in the specification through implicit or inherent disclosure. *See* MPEP 2163 IB.

In the present case, essentially the entire specification supports the step (d) as amended. As pointed out in Applicants' last Reply, support the RT or protease inhibitors as claimed is found on pages 20 and 28, and the entire specification clearly teaches that the disclosed protease inhibitors are currently available and useful for antiretroviral therapy. Inherent in a method of evaluating the effectiveness of an antiviral therapy of an HIV-infected patient is using such RT and protease inhibitors. At the time of the invention, the combinations enclosed in claim 7 were sufficient and complete to establish the effectiveness of the different HIV drug regimens available. Accordingly, the specification clearly contemplates and implicitly discloses the objected to matter.

Applicants respectfully request that the rejection of the claim 7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicant submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: June 16, 2005



Andrew T. Serafini
Registration No. 41,303

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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